Rapid Evidence Review

Tocilizumab in the management of COVID-19.

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National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

Prepared by the COVID-19 Evidence Review Group with clinical input from Dr Niall Conlon, Consultant Immunologist, St. James Hospital and Professor Michael O'Dwyer, Consultant Haematologist, Galway University Hospital.

Key changes (highlighted in yellow) between 4 (21st of August 2020) and version 5 (23rd of October 2020): Updated evidence (n=28 publications) relating to tocilizumab in COVID-19 added. Only RCTs and published prospective and retrospective studies with ≥100 patients treated with tocilizumab in COVID-19 (n=17) have been included in the evidence review update.

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Elevated inflammatory markers including IL-6 levels have been described in patients with severe COVID-19. Recently, two meta-analyses examined the role of IL-6 and suggested that IL-6 levels are significantly elevated in patients with COVID-19 and are associated with adverse clinical outcomes. Extrapolation of evidence from cytokine-driven hyperinflammatory-related disorders intimates that patients who have severe COVID-19 with hyperinflammation could benefit from tocilizumab. Overall, observational studies published to date have suggested that tocilizumab may be a promising candidate to improve the outcomes of patients with severe or critical COVID-19 infections and could have a role in moderate COVID-19. However, this evidence is predominantly from single centre, non-randomised studies with small sample sizes of sub-optimal methodological quality which are prone to various biases and structural limitations. The therapeutic benefit suggested in observational studies has not been replicated in randomised controlled trials. Interim results from the COVACTA trial, a randomised, double-blind, placebo-controlled phase III RCT in severe COVID-19 associated pneumonia, did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality at 28 days(1). A multicentre, open label, phase II RCT in Italy (RCT-TCZ-COVID-19 Study Group) also reported tocilizumab did not reduce the risk of clinical worsening as no differences in ICU admissions and mortality in patients with COVID-19 were observed when treated with tocilizumab compared with standard of care (2,3). The BACC study, a randomized, double-blind, placebo-controlled trial of tocilizumab administered relatively early in the disease course, has also concluded that tocilizumab does not demonstrate benefit in preventing disease progression as measured by intubation or death in moderately ill hospitalized patients with COVID-19 (4). In contrast with the results of the BACC and COVACTA studies, the CORIMUNO-TOCI-1 study, a multicentre, open-label, randomized, controlled trial which evaluated tocilizumab for the treatment of moderate or severe COVID-19 associated pneumonia suggests that that tocilizumab may reduce the need for mechanical and non-invasive ventilation or death by day 14 but not disease progression or mortality by day 28. Preliminary unpublished results from the EMPACTA study, a multicentre, randomized, double-blinded, placebo-controlled phase III trial also suggest that patients treated with tocilizumab were less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care. However, the study failed to meet any of the secondary endpoints including no difference in mortality at Day 28(5). The RECOVERY study is ongoing and is evaluating tocilizumab in patients with clinical evidence of a hyperinflammatory state and progressive COVID-19, with results expected in the coming weeks.

Conclusion

In contrast to observational studies, the emerging RCT evidence[1] for tocilizumab does not show clear evidence of efficacy in support of tocilizumab in COVID-19 (3,4,6). Tocilizumab has not demonstrated

[1] *Some of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints". These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.*

a significant difference in mortality outcomes at day 28 versus standard of care. Only two studies (CORIMUNO-19-TOCI-1 and EMPACTA) suggest that tocilizumab may reduce the need for mechanical ventilation in a subgroup of patients with severe COVID-19(5,6). No unknown increases side-effects have been observed in the tocilizumab arm over standard of care. Further trial results from the RECOVERY trial and the full peer-reviewed publication of the COVACTA and EMPACTA trials are awaited.

Introduction

Tocilizumab is a humanised anti-IL-6 antibody licensed for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and giant cell arteritis. It is also licensed for the induction of the rapid reversal of cytokine release syndrome (CRS), a form of cytokine storm caused by CAR-T treatment(7). Interleukin-6 (IL-6) is a key pro-inflammatory cytokine that is elevated in CRS. Suppression of pro-inflammatory interleukin-1 (IL-1) family members and IL-6 are likely to have a therapeutic effect in many inflammatory diseases, including viral infections (8). It has been suggested that the inhibition of IL-6 may help attenuate the CRS in severely ill patients with COVID-19 by reducing cytokine concentrations and acute phase reactant production (9,10). Tocilizumab prevents IL-6 from binding to soluble and cell associated IL-6 receptors inhibiting IL-6-mediated signalling (11).

In early December 2019 a novel enveloped RNA betacoronavirus was recognised as the cause of pneumonia cases of unknown origin. The virus is phylogenetically similar to SARS-CoV and has been designated SARS-CoV-2. Emerging studies highlight the characteristics of COVID-19 infected patients (12–15). Clinical data suggests that disease progression in COVID-19 infected patients may be driven by a dysregulated immune response resulting in a cytokine storm (16). Cytokine release syndrome (CRS) is a diverse set of conditions associated with the clinical phenotype of systemic inflammation, multi-organ failure, hyperferritinaemia and high mortality (17). The condition is associated with inflammation in a dysregulated positive feedback loop with elaboration of inflammatory cytokines including IL-6. In CAR-T cell-associated CRS, IL-6 is thought to be a key driver of symptoms (18). Several studies including two meta-analyses have suggested that IL-6 levels are significantly elevated in patients with COVID-19 and are associated with adverse clinical outcomes suggesting that IL-6 could potentially serve as an effective biomarker for predicting disease progression in patients with COVID-19 (19–25). Tocilizumab has shown efficacy for other iatrogenic causes of CRS and has demonstrated rapid improvements, typically within 48 hours of administration, in patients with CRS treated with CAR-T cells, for which it is licensed (18,26,27). Observational studies to date have suggested that tocilizumab may be an effective therapeutic strategy to counteract or dampen the intensity of the cytokine storm that may develop in conjunction with virally-induced ARDS in COVID-19 (28). Phase III studies to date have not demonstrated a reversal in CRS driven COVID-19 akin to the reversal of CRS from CAR-T cell infusion despite the suggested possible benefit (29).

Screening for hyperinflammation in patients with COVID-19 in which tocilizumab may be efficacious

The pathogenesis of COVID-19 remains unclear and there is no clear understanding of the molecular events which precipitate a cytokine storm (30). The identification of a unique definition of CRS during COVID-19 infection is crucial to better customize the management of critical patients (31). A correspondence from Mehta *et al* advocate active screening for hyperinflammation in patients with COVID-19 using the H score and trends in laboratory tests including increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate, to identify groups in whom targeted immunomodulation might improve mortality (16). However, Ritchie *et al* in further correspondence suggest that increased virus burden secondary to failure of the immune response to control infection drives inflammation; consequently, it is COVID-19 disease severity which requires correction, rather than the postulated hyperinflammation being an inappropriate host response. Ritchie *et al* further suggest that immunosuppression in patients with overwhelming viral illness therefore may be inadvisable as suppression of IL-6 could result in detrimental effects by inhibiting host anti-viral and anti-microbial immunity, which could result in delayed virus clearance and perpetuate the COVID-19 illness and potentially promote secondary bacterial infection (32).

Interleukin-6 in COVID-19

Although the mechanisms of COVID-19–induced lung injury are still being elucidated, the prevailing theory is that an excessive immune response induced by cytokine storm manifested by elevated IL-6 are key drivers of both lung damage and mortality in COVID-19 (33,34). It is unclear whether IL-6 represents a biomarker or a central pathogenetic element of severe COVID-19 that should be used as a parameter for therapeutic intervention. There is also a growing recognition of the uncertainty surrounding the role of IL-6 in CRS driven severe COVID-19. Sinha *et al* report an analysis of 5 cohorts of patients with COVID-19, each with more than 100 patients, and 3 cohorts of patients with ARDS and compared their IL-6 levels with median values typically reported in ARDS (36–41). They report that median IL-6 levels in patients with the hyperinflammatory phenotype of ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19 (42). Although IL-6 has been correlated with poorer health outcomes in COVID-19, elevated IL-6 cytokine levels alone does not prove causality. It therefore remains unclear whether IL-6 is a marker or a driver of severe COVID-19 pathophysiology or whether elevated IL-6 represents a part of a functioning adaptive immune response. Further data are necessary to determine whether IL-6 is a maladaptive or an adaptive inflammatory factor in COVID-19 pathogenesis. Recent studies have attempted to elucidate the appropriate prognostic level at which baseline IL-6 can predict invasive mechanical ventilation requirement, mortality risk and disease severity in patients with COVID-19 (43). Guirao et al report that IL-6 levels above 35 pg/mL increase both the risk of mortality (OR = 20.0, 95 % CI 4.214-94-912, p = 0.0001) and ICU admission (OR = 12.750, 95 % CI 2,159-75,3,3, p = 0.005). They suggest that a cut-off point of 35 pg/mL could help differentiate patients at increased risk of mortality as well as those who may develop more severe disease (35). However, the study is based on a small sample size (n=50) and does not take into account the limitations of IL-6 measurement as a prognostic tool or as a means of assessing response to treatment in COVID-19, as described by McElvaney et al. McElvaney et al highlight that immunometabolic comorbidities such as obesity can influence circulating IL-6 while IL-6 levels can vary within the same patient over the course of a day and the magnitude of IL-6 response to infection varies

between patients (44). Instead, they advocate the use of the Dublin-Boston score which has been developed to address the limitations associated with IL-6 serum measurement. The score uses the change between two IL-6:IL-10 ratio measurements taken 4 days apart to guide clinical decision-making by identifying hospitalised patients at risk of impending poor outcome, and is applicable to patients both in the ICU and on the ward. The authors report that the score, and the change in IL-6:IL-10 ratio from which it is derived, was shown to significantly outperform the predictive capabilities of IL-6 alone. However, the small sample size renders any results or outputs which are likely to be highly uncertain and subject to chance variation. This issue is compounded by their approach to analysis. Baseline assessment of interleukin levels (IL-6 and IL-10) were undertaken at day 0 (study entry) and were repeated thereafter which are not a meaningful or well-defined time point in terms of the COVID-19 disease course which renders the results difficult to interpret. It is also unclear from the study how patients with missing data or who were discharged or died prior to the end of the study were handled. The authors don't describe how they arrived at their linear score formula to generate the Dublin-Boston score which limits our ability to assess the appropriateness of this approach. Furthermore, the model which underpins the Dublin-Boston score has not yet been validated with external data, its use and therefore its predictive performance in clinical practice, should be considered exploratory. (44).

Critical appraisal of studies reporting the use of tocilizumab in COVID-19

A rapid critical appraisal of the phase III trial study results, the phase II trial results as well as published prospective and retrospective studies with n ≥100 patients treated with tocilizumab in COVID-19 was conducted by the ERG and are summarised in the following text.

Randomised controlled trials

Interim results from the COVACTA study which is a randomized, double-blind, placebo-controlled, phase III study of tocilizumab in hospitalized adult patients with severe COVID-19 associated pneumonia have been published but have not been peer-reviewed. In total 450 patients were randomized to receive a single dose of tocilizumab 8 mg/kg IV (maximum dose of 800 mg) or placebo along with current standard of care (SOC). One additional dose of tocilizumab could be given 8- 24 hours after the initial infusion if the clinical signs and symptoms worsened or did not improve, defined as worsened ordinal scale clinical status or persistent fever. SOC was defined as per local practice and may have included antivirals, low-dose steroids, convalescent plasma and supportive care. Key eligibility criteria were hospitalized patients with COVID-19 pneumonia confirmed using the WHO criteria (including a positive PCR of any specimen, i.e., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan and SPO_2 ≤93% or PaO_2/FiO_2 <300mmHg. The primary endpoint was Clinical Status Assessed Using a 7-Category Ordinal Scale [Time Frame: Day 28] which tracked patients' clinical status based on the need for intensive care and/or ventilator use, as well as supplemental oxygen requirements. Secondary endpoints included the difference in mortality, mechanical ventilation, time to hospital discharge and additional ICU variables at Week 4. An interim analysis was conducted indicating that the COVACTA trial had failed to reach its primary or secondary endpoints. The odds ratio for clinical status improvement at four weeks did not differ significantly between the study arms (odds ratio= 1.19, 95% CI 0.81 - 1.76, p=0.36). The authors suggest that as the primary analysis was conducted on Day 28 irrespective of COVID-19 disease duration and severity of illness it potentially missed clinical relevant differences between treatment arms. Mortality at 28 days

was 19.7% in the tocilizumab and 19.4% in the placebo group (p= 0.9410) and there was no significant difference in median time to hospital discharge or ventilator free days between study arms. It is noted that patients in the placebo arm received higher levels of co-treatment with steroids (54.9% vs 36.1%), antivirals (35.4% vs 29.6%), and convalescent plasma (4.2% vs 3.4%) than the tocilizumab arm during the study, however the imbalance is unlikely to have introduced bias towards lower mortality in the placebo arm as the mortality rate was higher in patients who received steroids in both study arms than in patients who did not received steroids which is contrary to the known survival benefit associated with steroid use in COVID-19 (1,45). The RECOVERY trial is not expected to terminate early as patients recruited to the study differ from those recruited to the COVACTA study. The RECOVERY trial considers the efficacy of tocilizumab in patients with severe COVID-19 whose disease has progressed with evidence of hyperinflammation while the COVACTA study did not consider evidence of hyperinflammation in the inclusion criteria (1,46,47).

Preliminary unpublished results from the EMPACTA (Evaluating Minority Patients with Actemra) study contrast with the results from the COVACTA study. The EMPACTA study was a multicentre, randomized, double-blinded, placebo-controlled trial phase III trial which evaluated the efficacy and safety of tocilizumab 8 mg/kg IV (maximum dose of 800 mg) compared with a placebo in combination with SOC in hospitalized participants with COVID-19 associated pneumonia. Key inclusion criteria were hospitalized patients with COVID-19 pneumonia confirmed using the WHO criteria (including a positive PCR of any specimen, i.e., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan and SPO_2 <94% while on ambient air who did not require non-invasive or invasive mechanical ventilation. The study population reflected patients that are often underrepresented in clinical trials largely from minority racial and ethnic groups across the Americas and Africa. The primary endpoint was the cumulative proportion of patients requiring mechanical ventilation by Day 28 or death. Key secondary endpoints include time to improvement of clinical status, time to clinical failure; defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first, mortality rate by Day 28, time to discharge, and adverse events. Study results were reported via press release on September 18th, 2020 indicating that the study met its primary endpoint as patients in the tocilizumab arm were 44% less likely to progress to mechanical ventilation or death by Day 28 compared to patients who received placebo plus standard of care (HR =0.56 95% CI 0.32 - 0.97, P=0.0348). However, the study failed to meet any of the secondary endpoints including no difference in mortality at Day 28 was observed (tocilizumab 10.4%, placebo 8.6%, difference 2%, 95% CI -5.2% to 7.8%). At Week 4, rates of infections and serious infections were 10% and 5% in the tocilizumab arm and 11% and 6.3% in the placebo arm, respectively. The EMPACTA study did not identify any new safety signals for tocilizumab. Although the results were announced in a press release, the results of this study are not yet available but are being submitted for publication in a peer reviewed journal (5).

Salvarani *et al* from the RCT-TCZ-COVID-19 Study Group (RCT-TCZ-COVID-19) report the findings from a phase II, multicentre, open-label, randomized clinical trial aimed at assessing the efficacy of early administration of tocilizumab versus SOC in hospitalized patients (n=126) with COVID-19 pneumonia across 24 Italian centres. Key inclusion criteria were a diagnosis of COVID-19 pneumonia confirmed by positive PCR in a respiratory tract specimen, the presence of mild acute respiratory failure (PaO_2/FiO_2 ratio between 200 and 300 mm/Hg), an inflammatory phenotype defined by a temperature greater than 38 °C during the last 2 days, and/or serum CRP ≥ 10 mg/dL and/or CRP level increased to at least twice the admission measurement. Patients were allowed to receive supplemental oxygen therapy,

but not invasive or non-invasive mechanical ventilation at study enrolment but were allowed to do so post randomisation. Key exclusion criteria were ICU admission and any condition preventing future admission to ICU, such as advanced age with multiple comorbidities or patient-expressed preference not to be admitted to ICU. The primary end point was clinical worsening within 14 days since randomization, defined by the occurrence of one of the following events, whichever occurred first i.e. admission to ICU with mechanical ventilation, death from any cause, PaO_2/FiO_2 ratio less than 150 mm Hg in one of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination. In cases of documented clinical worsening, patients could receive any therapy including steroids, while patients in the control arm were also eligible to receive tocilizumab therapy. Of note, 14 of 60 patients in the SOC arm received tocilizumab due to clinical worsening which may have impacted the study results. A protocol amendment was accepted by the ethics committee and an interim analysis for futility was conducted at one-third of the planned sample size (132 patients) due to challenges around participant enrolment due to a decrease in the incidence of COVID-19 disease in Italy. Investigators found no differences were observed in the occurrence of the primary composite end point between the tocilizumab and the control groups at 14 days (28.3% in the tocilizumab arm compared with 27.0% in the SOC arm showed clinical worsening within 14 days of randomisation (rate ratio = 1.05, 95% CI 0.59 – 1.86, p=0.87). The investigators also report no differences in ICU admission, discharge rates or death rates between arms, however it is noted that mortality rates at day 14 (1.7% versus 1.6%) and day 30 (3.3% vs 1.6%), and ICU admission rates at 14 days (10.0% vs 7.9%, respectively) were low in both tocilizumab and SOC arms, respectively (3). The low mortality rate is likely due to the trials exclusion criteria. The Italian Medicines Agency (AIFA) reported that the results did not highlight any benefit linked to the early administration of tocilizumab in patients with COVID-19 pneumonia and the study was terminated early. (2). Results from the TOCIVID-19 study which is a multicentre, single-arm, non-randomised, open-label, phase II study suggest that tocilizumab may offer a mortality benefit at Day 30 in patients with COVID-19. The authors suggest that the results should be hypothesis- generating given the significant limitations associated with this study including missing data and study design (48).

CORIMUNO-TOCI-1 is a multicentre, open-label, randomized, controlled trial which evaluated tocilizumab for the treatment of moderate or severe COVID-19 associated pneumonia across 9 treatment centres in France. Key inclusion criteria were a diagnosis of COVID-19 pneumonia confirmed by positive PCR and/ or by CT scan, with moderate or severe COVID-19 pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit upon admission to hospital. Patients recruited to the study were randomly assigned to receive tocilizumab (8 mg/kg), intravenously plus SOC on day 1 and on day 3 if clinically indicated or to receive SOC alone. SOC was defined as antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants which was provided at the discretion of the treating physicians. The primary outcomes assessed in the study were the proportion of patients dead or needing non-invasive or mechanical ventilation on day 4 (defined as scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS)); and survival with no need for non-invasive or mechanical ventilation at day 14. The day 4 and 14 outcomes were amended on April 6, 2020, to include high-flow oxygen in non-invasive ventilation to be consistent with the WHO-CPS definition. Prespecified secondary outcomes were clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to oxygen supply independency, biological factors such as C-reactive protein level, and adverse events. All analyses were performed on an intention-to-treat basis however no adjustment

for multiplicity was considered for secondary outcomes. Therefore, all analyses of the secondary endpoints should be considered exploratory and are not considered further in this review. Of 131 patients, 64 patients were randomly assigned to the tocilizumab arm and 67 to SOC arm; one patient in the tocilizumab arm withdrew consent and was not included in the analysis, and three patients did not receive tocilizumab due to death (n = 1), technical problems (n = 1), and patient refusal (n = 1). During the trial, antiviral drugs, glucocorticoids, and preventive or therapeutic anticoagulants were administered in 7 (11%), 21 (33%), and 59 (94%) patients, respectively, in the tocilizumab arm, and 16 (24%), 41 (61%), and 61 (91%) in the SOC arm, respectively. Additional immunomodulators were administered to one patient in the tocilizumab arm (anakinra) and four patients in the SOC group (anakinra, n = 3; eculizumab, n = 1). A subgroup analysis according to antiviral drug use at baseline was prespecified in the protocol. Analyses according to the use of corticosteroids were added post-hoc in light of the evidence published from the RECOVERY trial. The investigators used Bayesian statistical methods to assess efficacy. Treatment effect was expressed in terms of absolute risk difference (ARD) for the day 4 outcome and HR for the day 14 outcome. One of two predefined thresholds for treatment efficacy was met; the posterior probability of improved survival without the need for non-invasive or mechanical ventilation by day 14 in the treatment group was 95.05%, marginally exceeding the pre-specified threshold of efficacy (greater than 95%). However, tocilizumab did not reduce the risk of disease progression as there was no observed reduced risk of a WHO-CPS score of greater than 5 at day 4. The investigators suggest that tocilizumab may reduce the need for mechanical and non-invasive ventilation or death by day 14 but not disease progression or mortality by day 28. A key limitation of the CORIMUNO-TOCI-1 is the lack of blinding, open label study design and lack of placebo controls which may have influenced the clinical decision-making around need for subsequent therapeutic decisions including mechanical and non-invasive ventilation in the control arm. This may have impacted the results which suggest a reduced need for mechanical and non-invasive ventilation or death associated with tocilizumab. There is a second CORIMUNO study ongoing, CORIMUNO-TOCI 2, a trial conducted in patients with critical pneumonia, however results have not yet been published (6).

Stone *et al* report the results of the Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial; a randomized, double-blind, placebo-controlled study to evaluate the effects of tocilizumab compared to placebo on patient outcomes in participants (n=243) with confirmed SARS-CoV-2 infection and evidence of systemic inflammation. The hypothesis underlying the trial was that IL-6 receptor blockade in patients with disease that had not yet led to intubation would disrupt the cytokine storm associated with COVID-19, thereby preventing the most severe disease consequence. Patients were randomly assigned in a 2:1 ratio to receive SOC plus a single dose of either tocilizumab (8 mg/kg) (n=161) or placebo (n=81). The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses. The hazard ratio (HR) for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% CI 0.38 to 1.81). A comparable proportion of participants in the tocilizumab and placebo arms experienced the primary endpoint of intubation or death over 28 days of follow-up, with rates of 10.6% and 12.5%, respectively. Rates of clinical worsening on an ordinal scale were also similar in the two groups, at a corresponding 19.3% and 17.4%. Of note, patients in the tocilizumab arm (n=18) and the control arm (n=5) received other concomitant agents including remdesivir and glucocorticoids (excluding dexamethasone).The authors report that the findings from their study does not provide

support for the concept that early IL-6 receptor blockade is an effective treatment strategy in moderately ill patients hospitalized with COVID-19. Stone *et al* conclude that tocilizumab had no significant effect on the risk of intubation or death, on disease worsening, on time to discontinuation of supplemental oxygen, or on any of the efficacy outcomes examined. However, the investigators highlight that they cannot exclude the possibility that tocilizumab treatment is associated with either some benefit or harm in some patients because of the width of the confidence intervals for the efficacy comparisons (4).

Observational studies

Overall, observational studies published to date have suggested that tocilizumab may improve the outcomes of patients with severe or critical COVID-19 infections. However, the body of evidence published are predominantly single centre, non-randomised studies with small sample sizes of sub-optimal methodological quality which are prone to various biases and structural limitations. As such these are not as informative as well designed controlled RCT studies. Unlike randomised comparisons, observational studies cannot be used to draw causal inferences because of inherent known and unknown confounders which affect the results generated and our ability to interpret the results. Generally, observational studies included in this review have lacked the standard steps taken to minimise confounding such as prospective design, statistical adjustment for prognostic factors including propensity score matching, or stratification. Where statistical methods were employed to control for known confounders, unmeasured confounding cannot be ruled out. Observational studies assessed in this review have also highlighted that that key confounding factors are not always collected in a standardised way and there are often inconsistencies in terms of how data are classified and how missing data are handled.

There are limited observational data to suggest that tocilizumab may have a beneficial effect on clinical outcomes and survival if administered to patients outside of the ICU setting in the earlier stages of COVID-19 pneumonia (49–52). The definition of early stages of COVID-19 is study dependent as the aetiopathophysiology has not been elucidated to date. Some studies suggest that treatment with tocilizumab in patients with features of a cytokine storm may prevent progression to mechanical ventilation or death when compared against standard of care (51,53–56). In an observational study of 186 hospitalised patients with severe COVID-19 treated with tocilizumab through a compassionate use programme in Madrid, Spain, Gorgolas *et al* report that tocilizumab was more effective when administered to patients whose oxygen support was less than FiO_2 ≤0.5%, than when administered in more advanced stages of COVID-19 (FiO_2 >0.5%), with patients achieving lower rates of intubation or death (13% vs 37% respectively, p<0·001). However, it is noted that patients (n=21) who died within 24 hours after tocilizumab administration were excluded from the final analysis. The dose and timing of administration of tocilizumab was variable and clinical decisions regarding a patient's eligibility for intubation were decided by the hospital's committee; those with more severe disease are more likely to be intubated than those with less severe disease. It is also noted that the majority of patients (>90%) received concomitant treatment with low molecular weight heparin, and corticosteroids which may have influenced the study results (57).

In a retrospective analysis of 544 patients with severe COVID-19 in two centres in Italy, Guaraldi *et al* also report that tocilizumab may reduce the risk of invasive mechanical ventilation or death in patients

with severe COVID-19 pneumonia. All patients were treated with the standard of care (i.e., supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin), and a non-randomly selected subset of patients also received tocilizumab. After adjusting for sex, age, recruiting centre, duration of symptoms, and baseline Sequential Organ Failure Assessment (SOFA) score, intravenous or subcutaneous tocilizumab (n=179) was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020) versus standard of care treatment (n=365) (58). However, the lack of treatment concealment associated with tocilizumab in this open label study may have led to variability in clinical decision-making which can bias treatment outcomes reported in this study e.g. in a decision of when to move a patient to invasive ventilation or when progression to death/ ICU is imminent irrespective of the provision of treatments. In a single-arm, prospective, multicentre open label study of 63 hospitalised adult patients with severe COVID-19 in Italy, Sciascia *et al* report that tocilizumab administration within 6 days of admission to the hospital was associated with an increased likelihood of survival when compared with the administration of tocilizumab after the 7th day of admission (HR 2.2 95%CI 1.3 to 6.7, p<0.05) in patients (n=63) with severe COVID-19 (50). Tocilizumab was administered intravenously (n=34/65) or subcutaneously (n=29/65). The choice of route of administration of tocilizumab was based on drug availability only. The administration schedule including the timing, dosing and frequency of administration of tocilizumab was also unclear which may impact on outcomes, particularly when there are still questions regarding the appropriate time point of the disease course in which tocilizumab may confer benefit. The authors also do not report any clinical or laboratory prognostic variables which may aid the identification of patients in whom tocilizumab may confer benefit within the 6-day window of admission.

Gupta *et al* report the results from STOP-COVID, an US observational study of 4,485 adult COVID-19 patients admitted to ICUs at 68 U.S.-based hospitals from March 4th through May 10th. The investigators report that the risk of in-hospital mortality was lower in patients treated with tocilizumab in the first 2 days of ICU admission compared with patients whose treatment did not include early use of tocilizumab. Patients were stratified by whether they received tocilizumab during the first two day of ICU admission. The main outcomes were time to death and 30-day mortality. The final analysis included 3,924 patients (median age, 62 years; 62.8% were male), of whom 433 (11%) received tocilizumab. There were 1,544 deaths: 125 in the tocilizumab group and 1,419 in the no tocilizumab group (28.9% vs. 40.6%). Median follow-up was 27 days (IQR, 14-37), during which time tocilizumab patients had a lower mortality risk compared to with those not treated with tocilizumab (HR =0.71; 95% CI: 0.56 to 0.92). The estimated 30-day mortality was 27.5% (95% CI: 21.2% to 33.8%) in the tocilizumab-treated patients and 37.1% (95% CI: 35.5% to 38.7%) in the non-tocilizumab-treated patients (risk difference, 9.6%; 95% CI: 3.1% to16.0%). However, the authors acknowledge that the results should be considered preliminary until conclusive evidence is obtained from RCTs, due to the inherent susceptibility of observational studies to unmeasured confounding (59). Of note the study did not control for or collect any data on concomitantly administered medications including corticosteroids. Other studies have reported that there is no treatment benefit associated with tocilizumab in the severe COVID-19 disease setting.

A recently published systematic review and meta-analysis reports that there is no conclusive evidence that tocilizumab provides any additional benefit to patients with severe COVID-19 when compared to

placebo or control cohorts in terms of all-cause mortality, requirement for mechanical ventilation or risk of ICU admission (60). Colaneri *et al* report an analysis of critically ill patients with COVID-19 pneumonia who were prospectively enrolled in the SMAtteo Covid19 Registry (SMACORE) in Italy. Patients treated with tocilizumab (n=21) were matched using propensity scoring to patients treated with standard of care (SOC) (n=21). Both groups were treated with SOC which included a combination of hydroxychloroquine, azithromycin and a prophylactic dose of low molecular weight heparin. The authors report that the addition of tocilizumab did not significantly affect risk of ICU admission (OR 0.11; 95% CI 0.00 to 3.38; p = 0.22) or 7-day mortality rate (OR 0.78; 95% CI 0.06 to 9.34; p = 0.84) when compared with SOC in critically ill patients with severe COVID-19 pneumonia (29). Although the authors attempted to reduce bias through propensity score matching, unmeasured confounding cannot be ruled out as this procedure is unable to control for the effect of variables not included in the model which may be significant, given that the pathophysiology of COVID-19 is still unclear. The results of this study suggest that tocilizumab did not affect the risk of ICU admission or mortality rate in a cohort of 21 patients. However, this is a single centre, observational study with a small sample size, which could have limited the power of the analyses, and should not be extrapolated to conclude an absence of treatment effect. Price *et al* report the results of a single centre, retrospective observational study of patients with severe (n=94) and non-severe (n=59) COVID-19 treated with tocilizumab in a hospital in Connecticut, USA, guided by a hospital-based treatment algorithm that initially focused on patients with severe disease but evolved to target CRS. The authors hypothesised that patients treated for CRS, irrespective of disease severity (severe, ≥ 3 L supplemental oxygen to maintain oxygen saturation > 93%) at the time of admission, would have improved outcomes and that tocilizumab-treated patients with severe disease would have survival outcomes more like patients with less severe disease. Tocilizumab-treated patients with severe disease had higher baseline admission levels of high-sensitivity C-reactive protein (120 vs 71 mg/L; p = < .001) and received tocilizumab sooner (2 vs 3 days; p = < 0.001), but their survival was similar to that of patients with non-severe disease (83% vs 91%; p = 0.11), suggesting that the treatment of CRS with tocilizumab, rather than disease severity at admission, may play a key role in survival. The authors also observed that D-dimer levels increased in tocilizumab-treated patients and suggested that IL-6 receptor antagonism may interrupt only part of the hyperinflammatory response of CRS (61). A key limitation of this study includes the potential confounding from concomitant administration of glucocorticoids which was higher in the severe group (35%) than in the non-severe group (8.9%) which may have impacted on the reported treatment outcomes. The results should be considered preliminary, as they are from an uncontrolled series and a causal inference cannot be established. Of note, in a non-peer reviewed study, Marfella *et al* highlight their experience of tocilizumab in hyperglycaemic patients suggesting reduced effects relative to normoglycemic patients due to the higher baseline and persistent plasma IL-6 levels (62). Several case reports/series of interest report the experience of tocilizumab in renal transplant and liver transplant patients (63,64). However, these are single case observations and cannot be extrapolated as an indication or absence of treatment effect.

Timing and route of administration of tocilizumab

The timing of administration in relation to disease course remains uncertain and remains to be established. Of note, the extreme elevation of IL-6 levels in the aftermath of tocilizumab administration has been described, due to increased availability of IL-6 resulting from less binding to

the IL-6 receptor which suggests that IL-6 concentrations may not be a robust marker of disease activity in tocilizumab-treated patients (11). It has also been suggested that the timing of tocilizumab administration guided by IL-6 levels could be crucial for therapeutic efficacy. Squillace *et al* evaluated response to tocilizumab in a small cohort of patients (n=32) with COVID-19. The authors report that inflammation levels, as measured by serum IL-6, are a better of guide of when to initiate tocilizumab therapy than days from symptom onset. They also suggest that patients who demonstrated a high burden of inflammation (defined as IL-6 values >135 pg/ml) were associated with adverse clinical outcomes which suggests that tocilizumab may confer most benefit when serum IL-6 levels are less than 135 pg/ml. However, there are several limitations to this study including small sample size (n=32) and retrospective cohort design (65). It remains unknown at what level or time point IL-6 changes from having anti-viral properties to altering immunopathology in COVID-19. Clinical decisions regarding the timing to administer tocilizumab in retrospective observational cohort studies published to date highlight that decisions to treat have been predominantly driven by clinical parameters and biomarkers assumed to indicate IL-6 mediated immunopathology rather than being driven by a range or threshold of serum IL-6 levels. Studies published to date have not yielded any robust or conclusive evidence supporting an optimal timing of administration of tocilizumab in COVID-19.

Most studies in COVID-19 report that tocilizumab has been administered intravenously at a dose of 4-8mg/kg to patients with COVID-19 in line with its product licences for CAR-T cell induced CRS. More recently, some case reports have reported the use tocilizumab administered subcutaneously. Although there are data showing similar efficacy of tocilizumab administered intravenously or subcutaneously in rheumatoid arthritis, the pharmacokinetic and pharmacodynamic profile of tocilizumab in CRS is not well described. It is unclear whether the subcutaneous and intravenous routes of administration are interchangeable (66,67).

Safety of tocilizumab

There are limited safety data available for tocilizumab in this setting. Some studies have reported no increased risk of infection or adverse events (AEs) associated with tocilizumab (50,68). Other studies have suggested that treatment with tocilizumab might favour the persistence of the SARS-CoV-2 virus and iatrogenic infections (54). Kimmig *et al* reported that tocilizumab was associated with a higher incidence of secondary bacterial infections including hospital-acquired pneumonia and ventilator-associated pneumonia (64.3% vs. 31.3% p=0.010) in critically ill COVID-19 patients. However, it is plausible that patients receiving tocilizumab were sicker, had a worse prognosis and therefore more likely to acquire a secondary infection (69). Some case studies reported a potential risk of elevated hepatic enzymes and two cases of acute large bowel perforation in patients with COVID-19 pneumonia who received empiric tocilizumab (51,70). The RCT evidence from COVACTA indicated that there were similar proportions of patients experiencing AEs and serious AEs in the tocilizumab and SOC arm. While rates of infections were lower in the tocilizumab arm relative to SOC; rates of infections at 28 days were 38.3% and 40.6% in the tocilizumab and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the tocilizumab and placebo arms, respectively. Of note, there was only one case of an opportunistic infection in the tocilizumab (*Candida* sepsis) and SOC (respiratory moniliasis) arms. The COVACTA study did not identify any new safety signals for tocilizumab (1). The EMPACTA study did not identify any new safety signals for tocilizumab. Although

the results were announced in a press release, the results of this study are not yet available but are being submitted for publication in a peer reviewed (5). Salvarini et al from the RCT-TCZ-COVID-19 Study Group did not note any treatment related severe AEs associated with tocilizumab. The most common AEs reported were increased alanine aminotransferase level and decreased neutrophil count (3) Data from the CORIMUNO-TOCI-1 did not identify any new safety signals and no increase in adverse or serious AEs. The investigators report a lower rate of serious infections (n=2 in the tocilizumab arm, n=11 in the SOC arm) despite decreased neutrophil count and increased rate of neutropenia in the tocilizumab arm and suggest that these results might be explained by the decreased frequency of transfer to the ICU, and the more frequent use of steroid treatment (6).

Treatment guidelines

Treatment Guidelines which recommend the use of tocilizumab in COVID-19 which have been updated since July 2020.

Early iterations of international guidelines provided guidance on the dose and duration of tocilizumab for the treatment of COVID-19. More recently, the National Institute for Health (04/11/2020) and Infectious Disease Society of America (25/09/2020) recommended **against the use** of tocilizumab for the treatment of COVID-19, while Version 14 (30th October 2020) of the Belgian guidelines recommend that interleukin (6 or 1) blockers should only be used in clinical trials.

References

1. Rosas IO, Bräu N, Waters M, Go R, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. Z [Internet]. [cited 2020 Oct 29]; Available from: https://doi.org/10.1101/2020.08.27.20183442
2. AIFA. Studio randomizzato multicentrico in aperto sull'efficacia della somministrazione precoce del Tocilizumab in pazienti affetti da polmonite da COVID-19 17 giugno 2020 [Internet]. 2020 [cited 2020 Aug 21]. Available from: https://www.aifa.gov.it/documents/20142/1123276/studio_RE_Toci_17.06.2020.pdf/c32ed144-ce26-d673-6e4d-11d5d0d84836
3. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med [Internet]. 2020 Oct 20 [cited 2020 Oct 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33080005
4. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med [Internet]. 2020 Oct 21 [cited 2020 Oct 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33085857
5. Roche. Roche - Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia [Internet]. [cited 2020 Oct 29]. Available from: https://www.roche.com/investors/updates/inv-update-2020-09-18.htm
6. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med [Internet]. 2020 Oct 20 [cited 2020 Oct 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33080017
7. European Medicines Agency. EPAR RoActemra - EMEA/H/C/000955 - II/0086/G. 2019.
8. Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I, et al. Induction of Pro-Inflammatory Cytokines (IL-1 and IL-6) and Lung Inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-Inflammatory Strategies - PubMed. J Biol Regul Homeost Agents [Internet]. 2020 Mar 14 [cited 2020 Mar 24];34(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32171193/
9. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. medRxiv. 2020;
10. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med [Internet]. 2020 Mar 28 [cited 2020 Apr 14]; Available from: http://link.springer.com/10.1007/s00134-020-06022-5
11. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008 Nov 15;112(10):3959–64.
12. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020 Feb 28 [cited 2020 Mar 17];NEJMoa2002032. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2002032
13. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia].
14. Sun D, Li H, Lu X-X, Xiao H, Ren J, Zhang F-R, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr [Internet]. 2020 Mar 19 [cited 2020 Mar 24];1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32193831
15. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis [Internet]. 2020 Mar 16 [cited 2020 Mar 24]; Available

from: http://www.ncbi.nlm.nih.gov/pubmed/32176772
16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet [Internet]. 2020 Mar [cited 2020 Mar 16];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext
17. Behrens EM, Koretzky GA. Review: Cytokine Storm Syndrome: Looking Toward the Precision Medicine Era [Internet]. Vol. 69, Arthritis and Rheumatology. John Wiley and Sons Inc.; 2017 [cited 2020 Mar 17]. p. 1135–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28217930
18. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome [Internet]. Vol. 15, Expert Review of Clinical Immunology. Taylor and Francis Ltd; 2019 [cited 2020 Mar 17]. p. 813–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31219357
19. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020 Mar 29;105954.
20. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a Designated Infectious Diseases Hospital Outside Hubei Province, China. Allergy [Internet]. 2020 Apr 2 [cited 2020 Apr 9]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32239761
21. Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Medecine et Maladies Infectieuses. Elsevier Masson SAS; 2020.
22. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet [Internet]. 2020 [cited 2020 Apr 8];395:497–506. Available from: https://isaric.tghn.org/protocols/
23. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]. 2020 Mar 13 [cited 2020 Apr 8]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184
24. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. www.thelancet.com [Internet]. 2020 [cited 2020 Apr 8];395:507. Available from: https://doi.org/10.1016/
25. Pedersen SF, Ho Y-C. SARS-CoV-2: A Storm is Raging. J Clin Invest. 2020 Mar 27;
26. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies [Internet]. Vol. 20, Cancer Journal (United States). Lippincott Williams and Wilkins; 2014 [cited 2020 Oct 28]. p. 119–22. Available from: https://pubmed.ncbi.nlm.nih.gov/24667956/
27. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia. N Engl J Med [Internet]. 2013 Apr 18 [cited 2020 Oct 28];368(16):1509–18. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1215134
28. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet [Internet]. 2020 Mar [cited 2020 Mar 17];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext
29. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, et al. Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms [Internet]. 2020 May 9 [cited 2020 May 25];8(5):695. Available from: https://www.mdpi.com/2076-2607/8/5/695
30. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. Microbiol Mol Biol Rev. 2012 Mar 1;76(1):16–32.

31. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity Reviews. Elsevier B.V.; 2020. p. 102523.
32. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet [Internet]. 2020 [cited 2020 Apr 8]; Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30691-7/fulltext
33. Hedrick TL, Murray BP, Hagan RS, Mock JR. COVID-19: Clean up on IL-6 [Internet]. Vol. 63, American Journal of Respiratory Cell and Molecular Biology. American Thoracic Society; 2020 [cited 2020 Oct 28]. p. 541–3. Available from: www.who.int/emergencies/diseases/novel-coronavirus-2019/
34. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis [Internet]. Reviews in Medical Virology. John Wiley and Sons Ltd; 2020 [cited 2020 Oct 28]. Available from: /pmc/articles/PMC7460877/?report=abstract
35. Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. 2020 [cited 2020 Nov 5]; Available from: https://doi.org/10.1016/j.molimm.2020.10.006
36. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]. 2020 Mar 13 [cited 2020 Apr 9]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184
37. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis [Internet]. 2020 Jul 28 [cited 2020 Oct 28];71(15):762–8. Available from: https://pubmed.ncbi.nlm.nih.gov/32161940/
38. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054–62.
39. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet [Internet]. 2020 [cited 2020 Oct 28];395:1763–70. Available from: https://doi.org/10.1016/
40. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from two randomised controlled trials. Lancet Respir Med [Internet]. 2014 [cited 2020 Oct 28];2(8):611–20. Available from: https://pubmed.ncbi.nlm.nih.gov/24853585/
41. Sinha P, Delucchi KL, Thompson BT, McAuley DF, Matthay MA, Calfee CS. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. Intensive Care Med [Internet]. 2018 Nov 1 [cited 2020 Oct 28];44(11):1859–69. Available from: https://pubmed.ncbi.nlm.nih.gov/30291376/
42. Sinha P, Matthay MA, Calfee CS. Is a “cytokine Storm” Relevant to COVID-19? [Internet]. Vol. 180, JAMA Internal Medicine. American Medical Association; 2020 [cited 2020 Oct 28]. p. 1152–4. Available from: https://jamanetwork.com/
43. Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, et al. IL-6 serum levels predict severity and response to Tocilizumab in COVID-19: an observational study. J Allergy Clin Immunol [Internet]. 2020 Sep [cited 2020 Oct 29]; Available from: /pmc/articles/PMC7525244/?report=abstract
44. McElvaney OJ, Hobbs BD, Qiao D, McElvaney OF, Moll M, McEvoy NL, et al. A linear prognostic score based on the ratio of interleukin-6 to interleukin-10 predicts outcomes in COVID-19. EBioMedicine [Internet]. 2020 Nov 1 [cited 2020 Oct 28];61:103026. Available from: https://doi.org/10.1016/j.ebiom.2020.103026
45. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med [Internet]. 2020 Jul 17 [cited 2020 Oct 29]; Available from: https://pubmed.ncbi.nlm.nih.gov/32678530/

46. Roche. Actemra Use in Coronavirus Disease 2019 (COVID-19). 2020.
47. Nutfield Department of Population Health. Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial Protocol [Internet]. 2020 [cited 2020 Aug 21]. Available from: www.recoverytrial.net
48. Perrone F, Piccirillo MC, Ascierto PA, Salvarani C, Parrella R, Marata AM, et al. Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 prospective phase 2 trial * 1. Ist Naz Tumori [Internet]. [cited 2020 Aug 21];16. Available from: https://doi.org/10.1101/2020.06.01.20119149
49. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. 2020 [cited 2020 May 25]; Available from: https://doi.org/10.1016/j.ejim.2020.05.009
50. Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol [Internet]. 2020;1–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32359035
51. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev [Internet]. 2020 May 3 [cited 2020 May 25];102568. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32376398
52. Wadud N, Ahmed N, Shergil MM, Khan M, Krishna MG, Gilani A, et al. Improved survival outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome patients with Tocilizumab administration. medRxiv. 2020 May 16;2020.05.13.20100081.
53. Sinha P, Mostaghim A, Bielick CG, McLaughlin A, Hamer DH, Wetzler L, et al. Early administration of Interleukin-6 inhibitors for patients with severe Covid-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. Int J Infect Dis [Internet]. 2020 Jul 1 [cited 2020 Aug 21];99:28–33. Available from: https://doi.org/10.1016/j.ijid.2020.07.023
54. Quartuccio L, Sonaglia A, McGonagle D, Fabris M, Peghin M, Pecori D, et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care. medRxiv. 2020 May 10;2020.05.01.20078360.
55. Roumier M, Paule R, Groh M, Vallée A, Ackermann F. Interleukin-6 blockade for severe COVID-19. [cited 2020 May 26]; Available from: https://doi.org/10.1101/2020.04.20.20061861
56. Rimland CA, Morgan CE, Bell GJ, Kim MK, Hedrick T, Marx A, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States academic center. medRxiv. 2020 May 19;2020.05.13.20100404.
57. Gorgolas M, Cabello A, Prieto Perez L, Villar Alvarez F, Alvarez Alvarez B, Rodriguez Nieto MJ, et al. Compassionate Use of Tocilizumab in Severe SARS-CoV2 Pneumonia. When late administration is too late. medRxiv [Internet]. 2020 Jun 16 [cited 2020 Aug 21];2020.06.13.20130088. Available from: http://medrxiv.org/content/early/2020/06/16/2020.06.13.20130088.abstract
58. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol [Internet]. 2020 Aug 1 [cited 2020 Aug 20];2(8):e474–84. Available from: www.thelancet.com/rheumatology
59. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med [Internet]. 2020 Oct 20 [cited 2020 Oct 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33080002
60. Lan SH, Lai CC, Huang HT, Chang SP, Lu LC, Hsueh PR. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents. 2020 Jul 23;106103.

61. Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, et al. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients. Chest [Internet]. 2020 Jun [cited 2020 Aug 20];0(0). Available from: https://doi.org/10.1016/j.chest.2020.06.006
62. Marfella R, Paolisso P, Sardu C, Bergamaschi L, Angelo EC D', Barbieri M, et al. Negative impact of hyperglycemia on Tocilizumab therapy in COVID-19 patients. medRxiv. 2020 May 4;2020.04.29.20076570.
63. Hammami MB, Garibaldi B, Shah P, Liu G, Jain T, Chen P, et al. Clinical Course of COVID-19 in a Liver Transplant Recipient on Hemodialysis and Response to Tocilizumab Therapy: A Case Report. Am J Transplant [Internet]. 2020 May 2 [cited 2020 May 25];ajt.15985. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15985
64. Fontana F, Alfano G, Mori G, Amurri A, Tei L, Ballestri M, et al. COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. Am J Transplant [Internet]. 2020 May 13 [cited 2020 May 25];ajt.15935. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15935
65. Squillace N, Pozzi MR, Gustinetti G, Ricci E, Capici S, Columpsi P, et al. Therapy of Sars-Coronavirus-2 pneumonia: is there an optimal IL-6 cut-off for successful tocilizumab treatment? 2020;1–10.
66. Abdallah H, Hsu JC, Lu P, Fettner S, Zhang X, Douglass W, et al. Pharmacokinetic and Pharmacodynamic Analysis of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis From 2 Randomized, Controlled Trials: SUMMACTA and BREVACTA. J Clin Pharmacol. 2017;57(4):459–68.
67. Mazzitelli M, Arrighi E, Serapide F, Pelle MC, Tassone B, Lionello R, et al. Use of subcutaneous tocilizumab in patients with COVID-19 pneumonia. J Med Virol [Internet]. 2020 May 15 [cited 2020 May 25]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32410234
68. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. ChinaXiv [Internet]. 2020 Mar 5 [cited 2020 Mar 16]; Available from: https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf
69. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. medRxiv. 2020 May 20;2020.05.15.20103531.
70. Montorfano L, Miret R, Rahman AU, Alonso M, Maron DJ, Roy M, et al. Colorectal surgery obesity-related morbidity during COVID-19. Surg Obes Relat Dis. 2020 Jul 9;

Appendix 2: Clinical Trial Registers:

A search of the following clinical trial registers www.clinicaltrials.gov. The search highlighted that there are 75 clinical trials ongoing to assess the efficacy and safety of tocilizumab in COVID-19.

1. Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID19 (TACOS). A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19 (NCT04306705). Status: recruiting.
    - Primary outcome: Proportion of participants with normalization of fever and oxygen saturation through Day 14.
2. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (NCT04317092). This is a multicentre, single-arm, open-label, phase 2 study. Status: Active, not recruiting.
    - Primary outcome: One-month mortality rate
3. Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis. Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 Infection with Severe Multifocal Interstitial Pneumonia. An open label single group assignment study. (NCT04315480). Status: Active, not recruiting.
    - Primary outcome: arrest in deterioration of pulmonary function and improving lung function at 7 days.
4. A single arm open label study to assess tocilizumab in the prevention of Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE). Early Institution of Tocilizumab Titration in Non-Critical Hospitalized COVID-19 Pneumonitis (NCT04331795). Status: completed.
    - Primary outcome measures: Clinical response, and biochemical response
5. Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID). Pilot, Randomized, Multicentre, Open-label Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of SARS-CoV-2 Infection (COVID-19). NCT04332094. Status: recruiting
    - Primary outcome measures: In-hospital mortality, and need for mechanical ventilation in the ICU
6. Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT). A multicentre, double-blind, randomized controlled phase II trial. NCT04335071. Status: Terminated
    - Primary outcomes: Number of patients admitted to ICU, number of patients intubated, number of deaths,
7. A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia (COVACTA). A Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID19 Pneumonia NCT04320615. Status: completed.
    - Primary endpoint: Clinical Status Assessed Using a 7-Category Ordinal Scale at day 28.
8. Efficacy and Safety of Tocilizumab in the Treatment of SARS-Cov-2 Related Pneumonia (TOSCA) a Proof of Concept Study - NCT04332913. Status: recruiting.

- Primary endpoint: Percentage of patients with complete recovery defined as fever disappearance and return to normal peripheral oxygen saturation values (SpO2) after 14 days from the end of treatment with tocilizumab

9. Checkpoint Blockade in COVID-19 Pandemic (COPERNICO). NCT04335305. Status: recruiting.
    - Primary outcome: Percentage of patients with normalization of oxygen saturation by pulse oximetry (SpO2) ≥96% at day 14.
10. Prospective Study in Patients with Advanced or Metastatic Cancer and SARS-CoV-2 (COVID19) Infection (IMMUNONCOVID). Prospective, Controlled, Randomized, Multicentre Study to Compare the Efficacy of a Chloroquine Analog (GNS561), an Anti PD-1 (Nivolumab) and an Anti-interleukine-6 Receptor (Tocilizumab) vs Standard of Care in Patients With Advanced or Metastatic Cancer and SARS-CoV-2 (COVID-19) Infection NCT04333914. Status: suspended.
    - Primary outcome: 28-day survival rate
11. Personalised Immunotherapy for SARS-CoV-2 (COVID-19) Associated with Organ Dysfunction (ESCAPE). NCT04339712. Status: recruiting.
    - Primary outcome: Change of baseline total sequential organ failure assessment (SOFA) score, Improvement of lung involvement measurements and Increase of pO2/FiO2 ratio at day 8
12. Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID). A Prospective, Randomized, Factorial Design, Interventional Study to Compare the Safety and Efficacy of Combinations of Blockade of Interleukin-6 Pathway and Interleukin-1 Pathway to Best Standard of Care in Improving Oxygenation and Short- and Long-term Outcome of COVID19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome NCT04330638. Status: recruiting.
    - Primary endpoint: time to clinical improvement at day 15.
13. Anti-il6 Treatment of Serious COVID-19 Disease with Threatening Respiratory Failure (TOCIVID). An Open-Label, Multicentre Sequential and Cluster Randomized Trial NCT04322773. Status: Terminated.
    - Primary outcome: Time to independence from supplementary oxygen therapy (days from enrolment to 28 days)
14. CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC). Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patient NCT04331808. Status: active, not recruiting.
    - Primary outcomes: WHO progression scale at day 7 and 14, survival at day 14, 28 and 90 days, 28 day ventilator free days, respiratory acidosis at day 4, PaO2/FiO2 ratio from day 1 to 14, time to oxygen supply independency at 14 days, duration of hospitalisation to 90 days, time to negative viral excretion to 90 days, time to ICU discharge to 90 days, time to hospital discharge to 90 days.
15. Multi-centre, randomized, controlled clinical trial study of fapiravir tablets combined with tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). ChiCTR2000030894
    - Outcomes being assessed: clinical cure rate, viral conversion rate from positive to negative, duration of fever, lung imaging improvement time, rate of non-invasive and

invasive mechanical ventilation, mean length of stay, CPR, lymphocyte count (absolute and %).

16. Multicentre, randomized controlled clinical study of the efficacy and safety of tocilizumab in new coronavirus pneumonia (COVID-19). ChiCTR2000029765
    - Outcomes being assessed: cure rate, mortality, ventilator utilisation, length of stay
17. Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised COVID-19 Patients with High Risk of Progression. An Open-label, Randomized, Cross-over Interventional Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised COVID-19 Patients with High Risk of Progression. NCT04345445. Status: not yet recruiting.
    - Primary endpoint: The proportion of patients requiring mechanical ventilation and Mean days of ventilation
18. Tocilizumab for Prevention of Respiratory Failure in Patients with Severe COVID-19 Infection. A Phase II Study of IL-6 Receptor Antagonist Tocilizumab to Prevent Respiratory Failure and Death in Patients with Severe COVID-19 Infection. NCT04377659.
    Status: recruiting
    - Primary endpoint: Progression of respiratory failure or death
19. Efficacy of Early Administration of Tocilizumab in COVID-19 Patients. An Open-label Randomized Multicentre Study to Evaluate the Efficacy of Early Administration of Tocilizumab (TCZ) in Patients With COVID-19 Pneumonia. NCT04346355. Status: terminated.
    - Primary endpoint: Entry into Intensive Care with invasive mechanical ventilation or death from any cause or clinical aggravation
20. Serum IL-6 and Soluble IL-6 Receptor in Severe COVID-19 Pneumonia Treated with Tocilizumab (UHID-COVID19). Prognostic Value of Serum Interleukin-6 (IL-6) and Soluble Interleukin-6 Receptor (sIL-6R) in Severe Coronavirus Disease (COVID-19) Pneumonia Treated with Tocilizumab - a Prospective Single Centre Study (UHID-COVID19). NCT04359667. Status: not yet recruiting.
    - Primary endpoint: serum interleukin-6 and soluble interleukin-6 receptor as biomarkers of clinical outcomes in patients with severe coronavirus disease (COVID19) pneumonia treated with tocilizumab
21. The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation. NCT04377750. Status: recruiting.
    - Primary endpoint: One-month mortality rate.
22. A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia. A Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-Pneumonia. NCT04372186. Status: active, not recruiting.
    - Primary endpoint: Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28
23. Efficacy of Tocilizumab on Patients With COVID-19. Prospective, single-centre, placebo controlled, blinded, randomized controlled trial at MGH. NCT04356937. Status: active, not recruiting.

- Primary outcome: Proportion of patients that require mechanical ventilation at day 28.

24. A Study to Investigate Intravenous Tocilizumab in Participants with Moderate to Severe COVID-19 Pneumonia (MARIPOSA). A Phase-II, Open-Label, Randomized, Multicenter Study to Investigate the Pharmacodynamics, Pharmacokinetics, Safety, and Efficacy of 8 mg/kg or 4mg/kg Intravenous Tocilizumab in Patients with Moderate to Severe COVID-19 Pneumonia NCT04363736. Status: Completed.
    - A Primary endpoint: Concentration of C-Reactive Protein (CRP) at day 7.
25. Tocilizumab Treatment in Patients With COVID-19. Phase II, single-arm, open-label, prospective, blinded, clinical trial with Tocilizumab as the sole agent. NCT04363853. Status: recruiting.
    - Primary endpoint: blood chemistry, hematic biometry, blood gas, and thorax radiography at 25 hours, 48 hours and 7 and 14 days.
26. Tocilizumab Versus Methylprednisolone in the Cytokine Release Syndrome of Patients With COVID-19. Prospective randomized controlled phase 2 study. NCT04377503. Status: not yet recruiting.
    - A Primary endpoint: Patient clinical status 15 days after randomization
27. Assessment of Efficacy and Safety of Tocilizumab Compared to DefeROxamine, Associated with Standards Treatments in COVID-19 (+) Patients Hospitalized in Intensive Care in Tunisia (TRONCHER). Multicentric, Comparative, Randomized Study. NCT04361032. Status: not yet recruiting.
    - A Primary endpoint: 90-day mortality rate.
28. Tocilizumab for Patients with Cancer and COVID-19 Disease NCT04370834. Status: suspended.
    - Primary endpoint: frequency of response, length of time from level of care to step down level of care, survival up to 1 week. Status: suspended.
29. Favipiravir Combined with Tocilizumab in the Treatment of Corona Virus Disease 2019. A Multicenter, Randomized and Controlled Clinical Trial Study NCT04310228. Status: recruiting.
    - Primary outcome: clinical cure rate at 3 months.
30. Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-(SARS-CoV-2 Infection). An Open-Labelled, Randomized Phase 3 Trial NCT04361552. Status: withdrawn.
    - Primary outcomes: 7-day length of invasive mechanical ventilation (MV) and 30-day mortality rate.
31. Randomized Evaluation of COVID-19 Therapy (RECOVERY). A randomised, parallel assignment open label trial to evaluate COVID-19 therapy. NCT04381936. Status: recruiting.
    - Primary outcome: all-cause mortality within 28 days of randomisation.
32. Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19. A non-randomised, open-label, multi-centre prospective study. NCT04380818. Status: recruiting
    - Primary outcome: Efficacy of low-dose pulmonary irradiation assessed by change in PAFI O2 by 20% from day 2 after radiotherapy.
33. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP). Randomized, Embedded, Multifactorial Adaptive Platform Trial for

Community- Acquired Pneumonia NCT02735707. Status: recruiting.

- Primary outcomes: all-cause mortality (90 days), days alive and outside of ICU (to day 21)

34. The Fleming [FMTVDM] Directed CoVid-19 Treatment Protocol (FMTVDM). A randomised, factorial assignment trial. NCT04349410. Status: Completed.
    - Primary outcome: Improvement in FMTVDM Measurement with nuclear imaging
35. Plasma Exchange in Patients With COVID-19 Disease and Invasive Mechanical Ventilation: a Randomized Controlled Trial (REP-COVID). A multicentre open label randomized controlled clinical trial. Note tocilizumab is one of the listed comparators in the experimental arm. NCT04374539. Status: recruiting
    - Primary outcome: Impact of plasma exchange on mortality at 28 days.
36. An Open Randomized Study of Dalargin Effectiveness in Patients with Severe and Critical Manifestations of SARS-COVID-19. An Open Randomized Study of the Effectiveness of the Drug Dalargin for the Prevention and Treatment of Symptoms of Pulmonary Complications in Patients with Coronavirus Infection (SARS-COVID-19). An Open Randomized Study Note tocilizumab is one of the listed comparators in the experimental arm. NCT04346693. Active not recruiting
    - Primary outcomes: The change of viral load in patients with SARS-COVID-19 (baseline and day 10), The frequency of development of Acute Respiratory Distress Syndrome (ADRS) (through study completion), the frequency of early mortality (up to 30 days), the frequency of late mortality (up to 90 days), clinical status at the time of completion of participation in the study.
37. Ultra-Low Doses of Therapy with Radiation Applicated to COVID-19 (ULTRA-COVID). Note tocilizumab is one of the listed comparators in the experimental arm. NCT04394182. Status: recruiting.
    - Primary outcomes: oxygen therapy status at day 2, oxygen saturation at day 2.
38. Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS) (POPS or POP02). A prospective observational study. Note tocilizumab is listed as one of the treatments under evaluation. NCT04278404. Status: recruiting
    - Primary outcome measures: Clearance, volume of distribution, elimination rate constant, half-life, absorption rate constant, area under the curve, maximum concentration, time to achieve maximum concentration.
39. Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia. NCT04445272. Status: recruiting.
    - Primary outcome: To calculate the time of intubation [Time Frame: through study completion, and average of 1 month]. To calculate the time with oxygen therapy [Time Frame: through study completion, and average of 1 month]. To calculate the time with Non-invasive mechanical ventilation [Time Frame: through study completion, and average of 1 month]. To evaluate mortality rate [Time Frame: through study completion, and average of 1 month]

40. Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19. NCT04479358. Status: Recruiting.
    - Primary outcome: Time to Recovery [Time Frame: 28 days]
41. A RCT - Safety & Efficacy of Tocilizumab - Tx of Severe COVID-19: ARCHITECTS. NCT04412772Status: recruiting.
    - Primary outcome: Change in IL-12 values in the 3 study groups from the start of treatment (D0) and on days D + 1 and D + 3. [Time Frame: Day1 and Day3.].
42. Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01). NCT04435717. Status: recruiting.
    - Primary outcome: Clinical status (on a 7-point ordinal scale) at day 28 [Time Frame: up to day 28]
43. A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in Hospitalized Participants with Severe COVID-19 Pneumonia. NCT04409262. Status: recruiting.
    - Primary outcome: Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 28 [Time Frame: Day 28]
44. A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, to Compare Standard-of-care With Anakinra and Tocilizumab Treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study. NCT04412291. Status: recruiting.
    - Primary outcome: Time to recovery [Time Frame: Day 1 through Day 29].
45. A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association with RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease. NCT04424056. Status: not yet recruiting.
    - Primary outcome: Ventilation free days at D28 [Time Frame: 28 days].
46. Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIBRAS). NCT04403685. Status: Terminated.
    - Primary outcome: Evaluation of clinical status [Time Frame: Day 15 of the trial].
47. Tocilizumab Versus Dexamethasone in Severe Covid19 Cases. NCT04519385. Status: completed.
    - Primary outcome: survival [Time Frame: 14 days]
48. Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients with Covid-19. NCT04476979. Status: recruiting
    - Primary outcome: Survival without needs of ventilator utilization at day 14 [Time Frame: day 14].
49. Tocilizumab in Coronavirus-19 Positive Patients. NCT04423042. Status: not yet recruiting.
    - Primary outcome: All-cause mortality [Time Frame: Assessed at 30 days post treatment]
50. Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan. NCT04492501 Status: completed
    - Primary outcome: survival [Time Frame: 28 days]
51. Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 With Standard Therapy in Patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (COVID-19). NCT04380519. Status: Completed

- Primary outcome: Proportion of patients, responded to the study therapy, in each of the treatment groups [Time Frame: Day 15].

52. Convalescent Plasma Treatment in COVID-19. NCT04476888. Status: recruiting.
    - Primary outcome: Decrease length of stay [Time Frame: From date on which intervention given until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1 month]. Overall mortality [Time Frame: From date on which intervention given until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1 month]. Incidence of adverse events related to Convalescent Plasma transfusion [Time Frame: After receiving intervention (CP) till 24 hours].
53. Study on the Use of Sarilumab in Patients With COVID-19 Infection. NCT04386239. Status: not yet recruiting.
    - Primary outcome: Proportion of patients who show an improvement of the respiratory function [Time Frame: 6 weeks]
54. Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia. NCT04359095. Status: Recruiting.
    - Primary outcome: Mortality and Number of Participants with Treatment Related Severe Adverse Events as Assessed by the NCORP Guidance for Collection of Adverse Events Related to COVID-19 Infection [Time Frame: Post-intervention at day 28]
55. Factors Associated with Clinical Outcomes in Patients Hospitalized for Covid-19 in GHT-93 Est. NCT04366206. Status: recruiting
    - Primary outcome: Composite of death and mechanical ventilation [Time Frame: At 14-days follow-up]
56. Clinical Outcome of Anti-IL6 vs Anti-IL6 Corticosteroid Combination in Patients With SARS-CoV-2 Cytokine Release Syndrome. NCT04486521 Status: recruiting.
    - Primary outcome: Ventilator-Free Days [Time Frame: Up to Day 28
57. Effect of Treatments in Patients Hospitalized for Severe COVID-19 Pneumonia: a Multicenter Cohort Study. NCT04365764. Status: recruiting.
    - Primary outcome: Composite of death and mechanical ventilation [Time Frame: 14-days follow-up
58. Clinical Characteristics and Outcomes of 187 Critically Ill Patients with Coronavirus Disease 2019 (COVID-19). NCT04454372 Status: not yet recruiting.
    - Primary outcome: Outcome 30 days after ICU admission [Time Frame: 30 days after admission
59. Blood Ozonization in Patients With SARS-CoV-2 Respiratory Failure. NCT04388514. Status: recruiting.
    - Primary outcome: Time of respiratory improvement and earlier weaning from oxygen support [Time Frame: 3 days, 10 days]
60. A Systems Approach to Predict the Outcome of SARS-CoV-2 in the Population of a City; COVID-19. NCT04351503 Status: recruiting
    - Primary outcome: Identification of factors associated with (i) infection (binary, yes/no), (ii) hospitalization (binary, yes/no), (iii) requirement for ICU treatment

(binary, yes/no) [Time Frame: at baseline]. Duration of hospitalisations, duration of intensive care unit stays, in hospital mortality.

61. Glucocorticoids in COVID-19 (CORTIVID). NCT04438980 Status: recruiting
    - Primary outcome: Proportion of patients developing treatment failure (death, ICU admission, need for ventilator, Decrease in SpO2 <90% (in ambient air) or PaO2 <60 mmHg (in ambient air) or PaO2FiO2 <300 mmHg, associated with radiological impairment) [Time Frame: At 14 days after randomization]
62. Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease. NCT04392414 Status: Completed
    - Primary outcome: The number and proportion of patients with the normal body temperature (≤37.2 C) at the day 1, 2, 3, 4, 5, 6, 7 after the start of therapy [Time Frame: Days 1, 2, 3, 4, 5, 6, 7]
63. Conestat Alfa in the Prevention of Severe SARS-CoV-2 Infection in Hospitalized Patients With COVID-19. NCT04414631 Status: recruiting
    - Primary outcome: Disease severity [Time Frame: on day 7]
64. Clinical Efficacy of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection: a Randomized Clinical Trial. NCT04600141. Status: not yet recruiting
    - Primary outcome: Proportion of patients with clinical improvement [Time Frame: 30 days]
65. COVID-19: Salvage TOcilizumab as a Rescue Measure. NCT04577534. Status: recruiting
    - Primary outcome:
      Clinical status at day 28 [Time Frame: day 28]
66. Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers. NCT04403685. Status: terminated
    - Primary outcome: Evaluation of clinical status [Time Frame: Day 15 of the trial]
67. Tocilizumab in COVID-19 Lahore General Hospital. NCT04560205. Status: recruiting.
    - Primary outcome: Clinical response after administration [Time Frame: 10 days]
68. Cri Analog PG1 Effectiveness and Safety in Covid-19. NCT04536363. Status: not yet recruiting.
    - Primary outcome: Mortality [Time Frame: 6 month]
69. Evaluation of Therapeutic Effects of Melatonin by Inhibition of NLRP3 Inflammasome in COVID19 Patients. NCT04409522. Status: recruiting
    - Primary outcome: Melatonin [Time Frame: up to 10 days]
70. A Study of the Effectiveness of an Off Label Mefloquine Use for the Treatment of Patients With COVID19. NCT04347031. Status: active, not recruiting.
    - Primary outcome:
    - 1st primary endpoint for group 1 [Time Frame: up to 10 days]
        i The number of patients with development of respiratory failure requiring transfer to the ICU.
    - 2nd primary endpoint for group 1 [Time Frame: up to 10 days]
        i The period of clinical recovery.
    - 1st primary endpoint for group 2 [Time Frame: up to 10 days]
        i The period of clinical recovery.

- 2nd primary endpoint for group 2 [Time Frame: through study completion, an average of 3 months]
    i Frequency of fatal outcomes associated with coronavirus infection disease (COVID19)

71. Clinical Trial to Evaluate the Efficacy of Treatment With Hyperimmune Plasma Obtained From Convalescent Antibodies of COVID-19 Infection. NCT04366245. Status: recruiting.
    - Primary outcome:
    - Safety:
        i Incidence of Adverse Events and Serious Adverse Events grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE). [Time Frame: 30 days after enrollment]
        ii Incidence of Adverse Events and Serious Adverse Events grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE).
    - Efficacy:
        i Death from any cause [Time Frame: Day +21 after randomization]
        ii Need for mechanical ventilation [Time Frame: Day +21 after randomization]
        iii Any of the following analytical data after 72h of randomization. [Time Frame: Day +21 after randomization]
        iv IL-6> 80 pg / mL, D-dimer> 10 times, ferritin> 1000 ng / mL.
        v SOFA scale ≥ 3 after 72 hours of randomization or an increase of 2 points or more from the basal level [Time Frame: Day +21 after randomization]
72. Study of Open Label Losartan in COVID-19. NCT04335123. Status: completed
    - Primary outcome: Number of participants with treatment-related adverse events as assessed by protocol definition of AE [Time Frame: 14 days of losartan treatment]
73. Anti-SARS Cov-2 T Cell Infusions for COVID 19. NCT04401410. Status: not yet recruiting.
    - Primary outcome:
        i Graft versus Host Disease (GvHD) [Time Frame: 14 days post infusion or until treatment toxicity resolves]
        ii Cytokine Release Syndrome (CRS) [Time Frame: 14 days post infusion or until treatment toxicity resolves]
        iii Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) [Time Frame: 14 days or until treatment toxicity resolves]
        iv Adverse Events [Time Frame: 14 days post infusion or until treatment toxicity resolves]
        v Clinical Response Assessment: World Health Organization (WHO) Ordinal Scale [Time Frame: 7 Days or at time of hospital discharge]
74. Hemodynamic Impact on Critical Care Patients With Lung Damage Secondary to COVID-19. NCT04556864. Status: not yet recruiting.
    - Primary outcome: Total amount of hypotension [Time Frame: 5 days]

Appendix 4: Search strategy

A targeted literature review was conducted to inform the Rapid Evidence Review based on a search strategy developed by the Information Specialist at the National Centre for Pharmacoeconomics. A typical hierarchy of evidence was considered in the search, from highest to lowest:

- Systematic Literature Reviews and meta-analyses
- Randomized Controlled Trials
- Observational studies
- Published expert opinion

The landscape Review of International Clinical Guidelines identified up-to-date guidelines predominantly from other European countries and also China, the initial epicentre of the COVID-19 pandemic. Clinical trial registers in the EU, US and China were searched for evidence of ongoing or completed clinical trials.

Source	**Search**
Pubmed	(2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR ((Wuhan AND coronavirus) AND 2019/12[PDAT]:2030[PDAT])) AND ((((("tocilizumab" [Supplementary Concept]) OR "Antibodies, Monoclonal, Humanized"[Mesh]) OR "Interleukin-6"[Mesh] OR IL-6 OR IL6))
LitCovid	"Tocilizumab" OR "Interleukin-6" or "IL-6"
MedRxiv	"Tocilizumab" OR "Interleukin-6" or "IL-6"
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND “Tocilizumab”